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Dockets Management Branch (HFA - 305)
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 02D-0002; *Draft Guidance for Industry on Developing Drugs to Treat Inhalational Anthrax (Post-Exposure), 67 Federal Register 12021 (March 18, 2002)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2001 alone, Bristol-Myers Squibb dedicated $2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal regarding the development of drugs to treat inhalational anthrax (post-exposure).

Summary of BMS Comments on Proposal

We commend the U.S. FDA for providing this draft guidance to assist pharmaceutical companies in the development of antimicrobial drugs for the treatment of post-inhalation anthrax. However, there are several aspects of the proposed guidance that appear contrary to the FDA's stated objectives, which we have comments on as listed below.

I. Expansion of This Document

This guidance addresses the development of antimicrobial agents, that have had extensive post-marketing experience and ideally, with prolonged drug dosing safety information, for the prevention of disease in individuals exposed to *Bacillus anthracis* spores.

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Recommendation: While this document is a start towards identifying agents that could be effective in preventing the establishment of anthrax disease, similar guidance documents are needed for other bioterrorist indications (such as plague, tularemia, etc.), and for established anthrax infections (inhalational, gastrointestinal, and cutaneous).

Because *B. anthracis* strains resistant to penicillin and ciprofloxacin exist (either naturally or constructed *in vitro*), it would be prudent to identify compounds with potential usefulness in this indication prior to large-scale mass exposure to resistant strains. We recommend expansion of this guidance to include drugs in development and newly marketed agents, should they demonstrate advantages (i.e., in potency, PK, and/or lack of cross-resistance) over existing therapies. The use of a novel agent directed towards *B. anthracis* pathogenesis, and not directly on the organism itself, might influence the therapeutic approach and duration of treatment for this disease.

II. A Two-Tier Approval Process

Under Section V of the guidance, it states "This guidance serves as our best advice under the current scenario where approved therapies are available and the country is not in a state of massive-scale exposure to *B. anthracis.* In the event of a large-scale exposure or absence of other approved therapies (e.g., because of supplies are exhausted or otherwise unavailable), the Agency would provide emergency guidance on an alternative approach."

Recommendation: We suggest that approval of an antimicrobial agent for anthrax prophylaxis be a two-tier process. The first tier would include agents with: demonstrated *in vitro* potency; demonstrated PK/PD coverage, intracellular and tissue penetration; and demonstrated efficacy in a non-primate model of *B. anthracis* infection. Compounds in Tier 1 would be listed in the *In Vitro* only listing of the Microbiology Section, with possible added language indicating that the compound has not been tested in the monkey model and is not approved for post-inhalation anthrax. Language could also be added to the product label of newly introduced agents reflecting the absence of extensive post-marketing experience with the drug. The second tier would include agents with extensive post-marketing experience and have been tested in the monkey model. Agents in Tier 2 would be granted the indication for inhalation anthrax (post-exposure). Implementation of the two-tier approach would ensure availability of alternative therapies should current approved therapies for this indication become unavailable (either due to limited supply, or more importantly, be inactive against resistant strains). To wait for a large-scale exposure or depleted supply of approved therapies before consideration of alternative therapies is inconsistent with the pro-active measures taken against bioterrorism in this country.

If the Agency agrees to a 2-tier approval process, suggestion of acceptable efficacy models using small animals might be helpful.

III. Data on Prolonged Use

Under Section V (H), it mentions "there should be sufficient data on prolonged use of the drug in large numbers of patient."

Recommendation: It would be useful to define what is meant by 'prolonged.'

For the inhalation anthrax (post-exposure) indication, oral agents are preferred. Oral antibiotics are seldom developed to treat infections (such as endocarditis, osteomyelitis) requiring prolonged duration.

In the absence of prolonged use, would the Agency accept long-term pre-clinical animal toxicology results? Could the toxicity results in two animal species for up to 6 months provide the evidence needed for prolonged use of the drug in humans for this indication?

IV. Clinical Pharmacology Information

Under Section V (F), pharmacokinetic data of the drug in pregnant women and human breast milk were recommended.

Recommendation: This information is generally not collected with newer agents. This should be downgraded from a recommendation to a suggestion.

V. Microbiology Susceptibility Requirements

Under Section V(D), it says that "Testing should be done in at least two to three laboratories, and at least some of the same isolates should be tested by these laboratories to demonstrate reproducibility of MIC results." Strain Vollum, Ames, Sterne and others were among the common strains recommended for inter-laboratory testing.

Recommendation: We suggest that a common collection of *B. anthracis* strains consisting of Vollum, Ames, Sterne and other strains resistant to penicillin, ciprofloxacin, and/or doxycycline (either clinical or lab-constructed) be made available to laboratories licensed to do such testing. The CDC might maintain such a collection. A common set of strains from one source would ensure that findings generated on these isolates could be used for quality control purposes or for comparison of test results across studies.

VI. *In Vitro* Resistance Development

Under Section V(D), it states that "Efforts should be made to measure the potential for development of resistance in vitro. This testing should include studies to determine the frequency of spontaneous mutation and the emergence of multistep resistance in the presence of the compound."

Recommendation: We suggest that if *in vitro* resistance development rates are determined that this might be accomplished using avirulent strains of *B. anthracis.* Such strains might be accessible from a common source (such as the CDC) to allow for inter-laboratory comparison of test results. However, it must be appreciated that mechanisms leading to drug resistance in laboratory-derived strains might not mirror the resistance mechanisms encountered in naturally occurring resistant isolates. *In vitro* selection of resistant variants would not predict plasmid-mediated resistance. Therefore, one should be cautious in extrapolating resistance frequencies generated *in vitro* to the likelihood of resistance development clinically.

VII. The Monkey Model

The draft guidance indicates the need to perform a monkey study to gain approval of this indication.

Recommendation: We believe that the government (FDA or CDC) should establish a contract laboratory that could perform monkey efficacy studies with *B. anthracis*; this facility can in part be supported by sponsors requesting the testing of development compounds. With less than a handful of facilities capable of performing *in vivo* studies with *B. anthracis* and limited availability of monkeys, the requirement for monkey efficacy testing is currently the primary hindrance for approval of alternative therapies in post-inhalation anthrax.

Due to the limited resources (i.e., in testing facility and monkeys) available to perform the monkey study, we request that the Agency explore the marmoset, rabbit and septic mice models as alternative animal models for anthrax that might yield predictive efficacy information in man. Data generated in these small animal models, by investigators at USAMRIID and Porton Down, suggest that the non-primate models could provide relevant information on the human disease.

VIII. Recommended Antimicrobial Spectrum

Under Section V (G), one recommendation is that "The drug should be safe and effective in the treatment of a range of infectious disease due to a variety of pathogens."

Recommendation: It should be noted that potential agents for *B. anthracis* may not necessarily be broad-spectrum. Agents with limited activity against Gram-positive bacteria, or those specific to *B. anthracis* (such as a specific inhibitor of the *B. anthracis* protease) may be effective against this pathogen or its pathogenesis, despite their narrow antimicrobial spectrum. Moreover, the use of a narrow spectrum antibiotic could prevent the emergence of drug resistance of normal flora microbes, particularly when the drug is administered over a prolonged period, as is the case in post-inhalation anthrax.

IX. Postapproval Commitment / Requirement

Under Section V (L), it is suggested that in the event of an accidental or intentional exposure to aerosolized *B. anthracis,* the applicant should have a plan or approach to obtain confirmatory data. This information should be collected in cooperation with U.S.-based public health agencies.

Recommendation: We believe that the CDC should best handle the collection of such data. In the event of mass exposure to *B. anthracis* spores, the federal agencies called to the site would have better access to the exposed individuals and capacity to collect the necessary information.

X. Safety Data of the Drug in Pregnant women

One subpopulation of particular interest to the Agency is pregnant women. The Agency is interest in reviewing all available data on the safety of the drug in this population.

Recommendation: For most agents, there will be limited safety information of the drug in pregnant female. We suggest that preclinical reproductive toxicology data provide supportive evidence of drug safety in this population.

In summary, BMS recommends a two-tier approval process for the identification of agents that might be used to treat post-inhalation anthrax. Requiring the monkey efficacy study for drug approval in this indication is the primary limiting factor; perhaps, federal health agencies could certify or validate a contract laboratory capable of performing such studies. In addition, we recommend the use of animal data to support evidence of the drug's safe use in pregnant women and for its prolonged clinical use in humans.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie Smaldone

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